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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,696	10/31/2001	Donald Davies	2190/49927	8654

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,696	DAVIES, DONALD	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-82,84 and 85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-82,84 and 85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/3/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 1/30/04. Applicant's election without traverse of Group I (claims 41-82 and 84-85) in the amendment filed 1/30/04 is acknowledged. Claim 83 has been cancelled. Claims 41-82 and 84-85 are pending. An IDS filed 7/3/01 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Specifically, there is a sequence disclosed in Figure 6 that does not have a SEQ ID numbers associated with it. The sequence appears to be in the Sequence Listing, it would be remedial to amend the specification in the Brief Description of the Drawings by inserting the appropriate SEQ ID NO in the legend for Figure 6.

Claim Objections

Claims 61 and 77 are objected to because of the following informalities: In claim 61, line 2, "one" is written where it appears "are" should be written. In claim 77, line 2, "the" is duplicated prior to "gene encoding" and there is a period in the middle of the line 3. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 41-82 and 84-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These rejections are necessitated by applicant's amendment.**

Claims 41-82 and 84-85 are vague and indefinite in that the metes and bounds of "a gene or a part thereof encoding a polypeptide having p450 activity" are unclear. The specification does not define "p450 activity" and therefore it is not clear what criteria exist for identifying the polypeptides to be included in the invention or which biological activity is referred to by the term "p450 activity".

Claims 44-46 and 66-68 are unclear for reciting "viral based vector". A viral based vector is not defined by the specification or the prior art. It is unclear how much of the vector must be viral to be viral based or do specific viral components make the vector "viral-based". If specific viral components makeup the "viral-based vector", what components are required?

Claim 46 is vague and indefinite in that the metes and bounds of "a vector comprises at least one vector" are unclear. The claim implies that more than one vector might be included in the viral based vector, it is unclear how **a** vector can comprise more than a single vector.

Claim 48 is vague and indefinite in that the metes and bounds of "effective parts of at least two promoters" are unclear. It is not clear what constitutes "effective parts" of a promoter. For example, would a single nucleotide from one promoter operably substituted into a second promoter be considered an "effective part" of a promoter?

Claims 64 and 67-68 are vague in reciting "substantially". The term "substantially" is a relative one not defined by the claim, no single set of conditions is recognized by the art as being "substantial" and because the specification does not provide a standard for ascertaining the requisite degree, the metes and bounds of this claim cannot be established

Claim 68 recites the limitation "the viral based vector" in claim 64. There is insufficient antecedent basis for this limitation in the claim.

Claim 72 recites the limitation "said tumor-specific promoter" in claim 69. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-82 and 84-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claims read on a genus of vectors comprising genes or parts thereof encoding a polypeptide having p450 activity. As such, the claims read on a large genus of nucleic acids including genomic sequences that encode a large genus of proteins, or fragments thereof, that retain some activity associated with p450.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

In the instant case, applicants teach that "CYP1A2, also to a much lesser extent CYP2E1 and CYP3A4" are genes that encode a polypeptide having p450 activity (page 3, line 5-9). The cDNA for CYP1A2 is cloned and utilized in methods of analyzing *in vitro* the efficacy of cell killing using CYP1A2 in the presence of acetaminophen. Furthermore, applicants teach that CYP1A2 can convert acetaminophen into a metabolite called N-acetylbenzoquinoneimine (NABQI). However, there is no actual reduction to practice or clear depiction of what structures or properties are required for a "gene or part thereof" encoding a polypeptide having p450 activity. Neither applicant nor the prior art provide a correlation between the structure of CYP1A2 and it's activity. Given the diversity of genes and parts thereof and the inability to determine which parts will also have p450 activity, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Furthermore, in the instant case, applicants do not disclose any of the claimed genes. Applicants utilize the **cDNA** of CYP1A2 for cloning and expression purposes. The genomic version of any of the recited genes is not disclosed by the specification nor does the prior art

apparently disclose the entire gene. While the cDNA may be known, not all of the genes have been characterized. Because all of the components of the gene such as regulation sequences, introns, and exons must be determined empirically in order to generate the p450 genes, applicant claims the gene without sufficient disclosure about its structure. The skilled artisan would not conclude that applicant was in possession of viral vector comprising the claimed genes.

Claims 41-82 and 84-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 23 is rejected in so far as it reads on a host organism *in vivo*.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a composition comprised of acetaminophen and a vector encoding p450 and methods of using these compositions to treat cancer. The invention utilizes disciplines of molecular biology, virology and clinical technology.

2) **Scope of the invention**. The vector comprises a gene encoding a polypeptide having p450 activity, which converts acetaminophen into a metabolite called N-acetylbenzoquinoneimine (NABQI). Exposure of cancer cells to this metabolite leads to cytotoxicity. The invention recites use of this vector in conjunction with doses of acetaminophen that are lethal to cancer cells but not to normal liver cells. The method is directed toward gene therapy in mammals and humans using gene delivery protocols such as viral vector delivery. The only disclosed utility for practicing the claimed methods is for gene therapy. These steps of gene therapy exacerbate an already complex method.

3) **Number of working examples and guidance**. It is stated that administration of acetaminophen at high doses leads to levels of NABQI sufficient to kill cancer cells while normal liver cells are not killed. Purportedly, this is due to a difference in glutathione level in the cancer cells versus the liver cells (page 4, line 8-12). To further protect normal liver cells, it is suggested that a non-human p450 gene can be used in the invention in the presence of furaphylline, which inhibits function of human CYP1A2 (page 4, line 26-31). Methods are provided to increase the intracellular concentration of liver glutathione to detoxify NABQI and results from the administration of methionine and acetylcysteine. Applicants state that it might be possible to increase the efficiency of the system by replacing CYP1A2 with human CYP2E1 and CYP3A4 and rodent forms of these enzymes. However, other than human CYP1A2, the enzymes have not been analyzed.

Applicants assay the effects of p450 in the presence of acetaminophen using *in vitro* cell systems. The guidance for delivery of the vector to a mammalian subject is broad and general teachings i.e. administration includes but is not limited to intravenous, intramuscular,

intraperitoneal injection or direct injection into the tumour tissue (page 10, line 21-24). The instant specification fails to demonstrate any examples or specific guidance for introduction of the composition comprising a vector encoding a polypeptide having p450 activity and acetaminophen into a mammalian subject. There are no disclosures for *in vivo* concentration of vector or acetaminophen, no dose schedules and no determination of subjects for which the method would be directed. The instant examples are directed to methods of establishing stable and transient cell lines expressing p450. Experiments with transfected COS and H1A2 MZ cell lines demonstrate that *in vitro* acetaminophen in the presence of CYP1A2, leads to cell death. Variable bystander effects were identified in several cell lines incubated with stably expressing H1A2 MZ cells.

4) **State of Art**. The art of gene therapy for the treatment of cancer is a high art. Enormous efforts have been directed toward the development of gene therapy vectors and for cancer treatments. Each goal alone is complex and requires great skill in the art.

5) **Unpredictability of the art**. In general, many parameters must be addressed for *in vivo* gene delivery such as lack of toxicity to normal tissues, and the effect of the immune response as well as doses to be administered, dose schedules etc. The instant invention addresses the issue of cytotoxicity of cancer treatment to normal tissue. However, given the lack of *in vivo* experimentation, the data cannot be assessed. While *in vitro* models have been provided as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the

claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the *in vitro* transfection systems and the human disease state.

The unpredictable nature of gene therapy is exacerbated due to the lack of recited methods and because the genes are completely unknown at the onset as the invention. For example, while applicants disclose that cDNA encoding CYP1A2 can be used in the *in vitro* experimental system, the genes encoding polypeptides that have p450 activity are not disclosed. It is not clear that even if the genes were disclosed that the polypeptides encoded by the genes would function in a manner commensurate with that of the disclosed vector comprised of cDNA from CYP1A2. The route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al. (Verma et al. Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. The invention specifically recites use of viral vector s for delivery, use of viral vectors in gene therapy is highly unpredictable in the art. Meng and Deiry (Gene Therapy of Cancer, 1999, page 6, column 1) teach that means of delivery other than intratumoral injection compound the obstacles associated with adenoviral use. "Tropism for organs such as liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous of the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass". "While reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle positioned in a tumour deposit. This strategy achieves a relatively low efficiency of gene

delivery, which is confined to tumour cells immediately adjacent to the needle track. Plasmids or viral particles delivered in this way do not permeate freely through the interstitial fluid bathing the tumour." (Russell, p 1165, column 2). The level of infection necessary to achieve therapeutic affects of the heterologous gene without toxicity to normal cells that results from leaky expression of the viral genes required for replication is unknown. As noted by Marshall, (Marshall et al., Science January 17, 2003) one of the main issues in using retroviral vectors for gene therapy is determining how to use the vector in vivo without causing leukemia or other cancers in the patients being treated. This is not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and **use** the claimed invention for the recited treatments. No viral vector has proven adequate sources of gene delivery vehicles to date.

6) **Summary**. The invention recites a complex series of methods for the treatment of cancer using a vector encoding p450 and acetaminophen. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols and the inability to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan

would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER

Maria B Marvich, PhD
Examiner
Art Unit 1636